



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 9/00, 9/70</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/23011</b> <b>(43) International Publication Date:</b> 25 November 1993 (25.11.93)
<b>(21) International Application Number:</b> PCT/US93/04173 <b>(22) International Filing Date:</b> 3 May 1993 (03.05.93)  <b>(30) Priority data:</b> 07/885,282                      18 May 1992 (18.05.92)                      US  <b>(71) Applicant:</b> MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US). <b>(72) Inventors:</b> MCQUINN, Roy, L. ; BARKHAUS, Joan, K. ; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). <b>(74) Agents:</b> REEDICH, Douglas, E. et al.; Intellectual Property Counsel, Minnesota Mining and Manufacturing Company, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).		<b>(81) Designated States:</b> JP, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> TRANSMUCOSAL DRUG DELIVERY DEVICE  <b>(57) Abstract</b>  A transmucosal drug delivery device in the form of a sheet material. The device contains an acid-containing particulate polymeric resin dispersed throughout a polytetrafluoroethylene support matrix.		

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TRANSMUCOSAL DRUG DELIVERY DEVICEBACKGROUND OF THE INVENTION5 Field of the Invention

This invention relates to mucosal adhesives. In another aspect this invention relates to compositions that adhere to oral mucosa. In yet another aspect this invention relates to methods of  
10 transmucosal drug delivery.

Description of the Related Art

Buccal tablets and like devices are known and disclosed for example in U.S. Pat. Nos. 4,740,365  
15 and 4,764,378. These devices adhere to mucosal surfaces and dissolve or otherwise disintegrate over time, thus delivering drug into the mouth of the patient in a sustained fashion. It is also known that delivery of drugs across the oral mucosa avoids hepatic  
20 first-pass inactivation, inactivation by gastro-intestinal fluids, and other modes of inactivation characteristic of oral drug ingestion. Sustained release adhesive bandages, patches, and the like that contain drugs and adhere to mucosal surfaces  
25 are known to the art.

SUMMARY OF THE INVENTION

This invention provides a transmucosal drug delivery device in the form of a sheet material having  
30 a surface intended to be adhered to a mucosal surface, comprising:

- 1) a particulate polymeric resin comprising carboxylic acid containing monomer units and having an average particle size of  
35 less than or equal to about 100  $\mu\text{m}$ ;
- 2) from about 10 parts to about 200 parts by weight of a polytetrafluoroethylene support

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matrix based on 100 parts by weight of the resin; and

3) an amount of a drug effective to provide a desired therapeutic result;

5           which composition contains less than about 10% water by weight based on the weight of the polymeric resin, and adheres to a mucosal surface for a time sufficient to release the drug to the mucosal surface.

10           A device of this invention exhibits good adherence to human oral mucosa. Also, the drug is released in sustained fashion over a prolonged period to a mucosal surface or to the vicinity of a mucosal surface for, for example, local or systemic treatment.

15           In a preferred embodiment the device further comprises a flexible film backing adhered to one side of the device.

            This invention also provides therapeutic methods. One such method is a method of achieving  
20   and/or maintaining a therapeutically effective blood level of a drug in a mammal, comprising the steps of:

            a) adhering a device of the invention to a mucosal surface of a mammal; and

            b) allowing the device to remain adhered for  
25   a time sufficient to release the drug such that a therapeutically effective blood level of drug is achieved and/or maintained.

            Another such method is a method of delivering a drug to a mucosal surface of a mammal or to the  
30   vicinity of a mucosal surface of a mammal to provide a therapeutic effect on or in the vicinity of the mucosal surface, which method comprises the steps of:

            a) adhering a device of the invention to the mucosal surface;

            b) allowing the device to remain adhered for  
35   a time sufficient to release the drug to the mucosal surface or to the vicinity of the mucosal surface to provide the desired therapeutic effect.

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A device of the invention can be used to administer drugs systemically (e.g., across the oral or vaginal mucosa or other mucosal surfaces) or locally (e.g., to the oral or vaginal cavity). A device of the invention exhibits sustained delivery of basic, acidic, and neutral drugs, and salts thereof and allows the delivery rate to be tailored as desired. In the case of delivery of a drug across the oral mucosa, a device of the invention can also minimize the loss of a drug to the gastro-intestinal tract. A device of the invention is also soft and conformable such that it can be worn comfortably by the user.

#### Detailed Description of the Invention

The polymeric resin component of a device composition of the invention comprises monomer units containing carboxylic acid moieties. The resin preferably comprises at least about 55% by weight of carboxylic acid moieties based on the total weight of the resin. Suitable carboxylic acid-containing monomers include acrylic acid, maleic acid, itaconic acid, citraconic acid, methacrylic acid, and the like, and combinations thereof. Acrylic acid is preferred. The polymeric resin can also comprise minor amounts (e.g., less than about 20 percent by weight based on the total weight of all monomers in the polymer) of comonomers that are polymerizable with the carboxylic acid-containing monomer, such as methyl vinyl ether, lower alkyl (meth) acrylates, and the like.

Linear polyacrylic acid resins with a molecular weight between about 400,000 and about 5,000,000 have been found to be suitable for use in a composition of the invention. More preferred, however, are crosslinked resins. Most preferred resins include those comprising polyacrylic acid with a molecular weight between about 750,000 and about 4,000,000, preferably about 2,000,000 to about 4,000,000, and more preferably about 3,000,000, crosslinked with about

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0.75% to about 2% by weight, based on the total weight of the resin, of a polyalkenyl polyether such as an allyl ether of sucrose or an allyl ether of pentaerythritol. Particularly preferred resins of this type include the resins available under the trade designation CARBOPOL™ resin (e.g., CARBOPOL™ resins 910, 934, 934P, 941, 951, and 1342 from B.F. Goodrich Co., Specialty Polymers and Chemical Division, Cleveland, OH). CARBOPOL™ 934P resin is most preferred, as it is generally recognized as acceptable for pharmaceutical applications. Another suitable resin is "polycarbophil", a material commercially available from A. H. Robins Co., Richmond, Virginia, and described in USP XX as a polyacrylic acid crosslinked with divinylglycol.

A polyacrylic acid resin or a crosslinked resin such as those enumerated above can be partially neutralized by a base of an alkali metal, or by a base of a divalent or trivalent metal (e.g.,  $\text{Zn}^{+2}$ ,  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$ , or  $\text{Al}^{+3}$ ). Basic polyamines such as EUDRAGIT™E (a copolymer of dimethylaminoethyl methacrylate and neutral methacrylates, available from Rohm Pharma, Weiterstadt, Germany) are also suitable for use in neutralizing a resin. In such a resin, up to about 30% of the carboxylic acid moieties in the resin can be neutralized by a base. Preferred bases include  $\text{Al}(\text{OH})_3$  and  $\text{Ca}(\text{OH})_2$ .

It is preferred that the resin have an average particle size of between about 1  $\mu\text{m}$  and about 80  $\mu\text{m}$ , more preferably between about 1  $\mu\text{m}$  and about 30  $\mu\text{m}$ , and most preferably between about 2  $\mu\text{m}$  and about 10  $\mu\text{m}$ .

It is desirable to keep the level of moisture low in a device of the invention. A device of the invention has a water content of less than about 10% by weight, preferably less than about 6%, more preferably less than about 4% by weight, and most preferably less than about 2% by weight based on the total weight of

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the resin. In order for the composition to have the requisite low water content the resin, prior to incorporation in the composition, is preferably dried to the desired level and protected from ambient moisture. Once the resin is incorporated in a composition of the invention, ambient moisture is no longer generally of concern, as the resin, which is generally hygroscopic, is protected from ambient moisture by the support matrix (described below). A device can be stored for at least several months at ambient humidity without adversely affecting its adhesive properties.

By itself, a polymeric resin as described above generally possesses insufficient structural integrity. Such acidic resins can also be irritating to mucosal tissue. Further, a resin alone provides no means of controlled hydration and sustained release of drug. To remedy these deficiencies, device further comprises a polytetrafluoroethylene support matrix. The resin is preferably substantially dispersed throughout the polytetrafluoroethylene support matrix.

The relative amounts of the polymeric resin and the polytetrafluoroethylene support matrix can affect both the duration of adhesion and the drug release properties of a composition of the invention. Generally a composition of the invention comprises about 10 parts to about 200 parts, preferably about 10 parts to about 100 parts, and most preferably 15 to about 50 parts by weight of a polytetrafluoroethylene support matrix, based on 100 parts by weight of the resin.

The support matrix is preferably in the form of a polytetrafluoroethylene (PTFE) web. Such webs having particulate material substantially uniformly dispersed therein are disclosed in, e.g. U.S. Pat. Nos. 4,153,611 (Ree et al.), 4,373,519 (Errede et al.), and 4,906,378 (Hagen et al.). The polytetrafluoroethylene

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web is soft such that the device can be worn without significant discomfort to the user.

A device of the invention also comprises a drug. Drugs that can be delivered include those useful for the local treatment of the mouth or throat, or the vaginal cavity, in addition to those useful for systemic treatment via delivery through mucosal tissue. They include antiinflammatory drugs, both steroidal (e.g., hydrocortisone, prednisolone, triamcinolone) and nonsteroidal (e.g., naproxen, piroxicam); bacteriostatic agents (e.g., chlorhexidine, hexylresorcinol); antibacterials (e.g., penicillins such as penicillin V, cephalosporins such as cephalexin, erythromycin, tetracycline, gentamycin, sulfathiazole, nitrofurantoin, and quinolones such as norfloxacin, flumequine, and ibafloxacin); antiprotazoals (e.g., metronidazole); antifungals (e.g., nystatin); coronary vasodilators (e.g., nitroglycerin); calcium channel blockers (e.g., nifedipine, diltiazem); bronchodilators (e.g., theophylline, pirbuterol, salmeterol, isoproterenol); enzyme inhibitors such as collagenase inhibitors, protease inhibitors, elastase inhibitors, lipoxxygenase inhibitors (e.g., A64077), and angiotensin converting enzyme inhibitors (e.g., captopril, lisinopril); other antihypertensives (e.g., propranolol); leukotriene antagonists (e.g., ICI204,219); anti-ulceratives such as H2 antagonists; steroidal hormones (e.g., progesterone, testosterone, estradiol); antivirals and/or immunomodulators (e.g., 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinoline-4-amine, and other compounds disclosed in U.S. Pat. No. 4,689,338, acyclovir); local anesthetics (e.g., benzocaine, propofol); cardiotonics (e.g., digitalis, digoxin); antitussives (e.g., codeine, dextromethorphan); antihistamines (e.g., diphenhydramine, chlorpheniramine, terfenadine); narcotic analgesics



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(e.g., morphine, fentanyl, buprenorphine); peptide hormones (e.g., human or animal growth hormones, LHRH); cardioactive products such as atriopeptides; proteinaceous products (e.g., insulin); enzymes (e.g., anti-plaque enzymes, lysozyme, dextranase); antinauseants (e.g., scopolomine); anticonvulsants (e.g., carbamazine); immunosuppressives (e.g., cyclosporine); psychotherapeutics (e.g., diazepam); sedatives (e.g., phenobarbital); anticoagulants (e.g., heparin); analgesics (e.g., acetaminophen); antimigraine agents (e.g., ergotamine, melatonin, sumatripan); antiarrhythmic agents (e.g., flecainide); antiemetics (e.g., metaclopramide, ondansetron); anticancer agents (e.g., methotrexate); neurologic agents such as anxiolytic drugs; hemostatics; anti-obesity agents; and the like, as well as pharmaceutically acceptable salts and esters thereof.

The drug is present in a therapeutically effective amount, which will depend upon the particular drug used, the intended therapy, and the desired duration of use of a particular individual device containing the drug. Practical limitations on the amount of drug are that amount above which the composition begins to lose adhesion to a mucosal surface, and that amount below which a therapeutically effective blood level of drug cannot be achieved and/or maintained. Generally, the preferred range is from about 0.1% to about 25% by weight based on the total weight of the device. Preferably, the drug will be capable of release from the device in a sustained fashion over a prolonged period (i.e., at least about 6 hours and preferably at least about 12 hours).

A device of the invention preferably comprises a flexible film backing on one side of the device. The backing is preferably a flexible film that prevents bulk fluid flow and is inert to the ingredients of the device. The backing protects the

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composition from excessive swelling and loss of  
adhesion over the time period during which the  
composition is intended to remain adhered to the  
mucosal surface. In the case of a device that contains  
5 a drug intended to be delivered to or across a mucosal  
surface (as opposed to delivery to the vicinity of the  
mucosal surface, e.g., to the oral cavity), the film  
backing material is preferably substantially  
impermeable to the drug and therefore it effectively  
10 prevents migration of the drug out of the coated  
portion of the device. In the case of a device that  
contains a drug intended to be delivered, e.g., to the  
oral cavity or the vaginal cavity, the backing can be  
permeable to the agent to be delivered and can be  
15 permeable to saliva as well.

The backing can be any of the conventional  
materials used as backing for tapes or dressings, such  
as polyethylene, polypropylene, ethylene-vinyl acetate  
copolymer, ethylene propylene diene copolymer,  
20 polyurethane, rayon, and the like. Non-woven materials  
such as polyesters, polyolefins, and polyamides can  
also be used. Also, a layer of a hydrophobic elastomer  
such as polyisobutylene can function as a backing.  
Preferred backing materials include an acrylate  
25 pressure-sensitive adhesive coated polyurethane film  
such as TEGADERM™ brand surgical dressing (commercially  
available from the 3M Company, St. Paul, MN).

The most preferred flexible film backings  
occlude substantially all of the surface area of the  
30 patch other than that surface that is intended to be  
adhered to the mucosal surface, while the surface of  
the patch that is to be adhered to the mucosal surface  
is substantially free of the backing. When the device  
is in use there is substantially no uncoated surface  
35 area of the device (such as uncoated sides or edges)  
exposed to mucus into which the drug can be delivered  
inadvertently.

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The most preferred backing materials are also substantially insoluble in mucus and other fluids endogenous to the mucosal surface (e.g., in a device intended to adhere to buccal mucosa or other oral mucosa the backing is substantially insoluble in saliva). "Substantially insoluble" as used herein means that a thin coating (e.g., 0.1 mm thick) of the film backing material will not be eroded such that areas become exposed when a device is in place on a mucosal surface for a period of several hours.

The most preferred film backing materials include those that can be taken up in solution or suspension and applied (e.g., by brushing, spraying, or the like) from solution or suspension, and those that can be applied in the form of liquid prepolymeric systems and subsequently cured. These preferred film backing materials include polymeric materials and polymeric systems that are commonly used as enteric coatings or controlled release coatings. Exemplary materials include cellulose derivatives (e.g., ethylcellulose, cellulose acetate butyrate, cellulose acetate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, chitin, chitosan), polyvinyl alcohol and derivatives thereof such as polyvinyl acetate phthalate, shellac, zein, silicone elastomers, and polymethacrylates (e.g., cationic polymers based on dimethylaminoethyl methacrylate such as those copolymers available as EUDRAGIT™ type E, L, and S copolymers, copolymers of acrylic and methacrylic acid esters containing quaternary ammonium groups such as those copolymers available as EUDRAGIT™ type RS and RL copolymers, and others known to those skilled in the art). Most preferred backing materials include zein and ethylcellulose.

A device can contain other ingredients, for example excipients such as flavorings or flavor-masking agents, dyes, penetration enhancers, water-soluble or water-swellaable fibrous reinforcers, and the like under

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circumstances and in amounts easily determined by those skilled in the art. Penetration enhancers have particular utility when used with drugs such as peptides and proteins. Suitable penetration enhancers

5 include anionic surfactants (e.g., sodium lauryl sulfate); cationic surfactants (e.g., cetylpyridinium chloride); nonionic surfactants (e.g., polysorbate 80, polyoxyethylene 9-lauryl ether, glyceryl monolaurate); lipids (e.g., oleic acid); bile salts (e.g., sodium

10 glycocholate, sodium taurocholate); and related compounds (e.g., sodium tauro-24,25-dihydrofusidate).

A resin useful in a composition of this invention can be prepared using conventional procedures and conventional laboratory equipment. For example,

15 such resins can be prepared from acrylic acid and the appropriate crosslinkers by methods well known to those skilled in the art, and disclosed for example in U.S. Pat. No. 2,798,053 (Brown). A commercially available polyacrylic acid resin or a commercially available

20 particulate resin such as the CARBOPOL™ resins discussed above can be used as received if it is available in an appropriate particle size and with a suitably low water content.

Conventional drying methods, preferably using

25 temperatures less than about 95°C, and more preferably less than about 50°C, can be used to dry a resin to the desired degree, e.g., less than about 2% water content. Further, if it is desired to increase or decrease the particle size, a resin can be wet-granulated by first

30 wetting and stirring with a polar solvent (e.g., isopropyl alcohol), drying to the desired degree (e.g., in a tray oven), and then milling to a powder of the desired size. Particle size can also be adjusted by other conventional techniques, with the caveat that

35 substantial degradation of the resin is to be avoided.

A neutralized resin as discussed above can be prepared as described in Patent Application WO 90/06505.

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A drug, a suitable resin, and any excipient or other ingredient can be formulated into a device according to the general methods set forth in U.S. Pat. No. 4,153,661 (Ree et al.). The methods disclosed in  
5 said patent involve the use of an aqueous PTFE formulation. The use of an aqueous PTFE formulation, however, results in severe swelling of the resin and the composition sticks to the mill roll when it is milled. Moreover, as devices of the invention contain  
10 less than about 10 percent by weight water based on the weight of the resin, drying to the desired level can be difficult and/or time consuming. Accordingly, it is preferred to use a method that avoids the use of water or a solvent that swells the resin. A preferred method  
15 involves combining the resin, the drug, and any excipient or other ingredient with dry PTFE particles having an average particle size of about 300  $\mu\text{m}$  to about 1000  $\mu\text{m}$ . A drug and any excipient or other ingredient can be incorporated by first adding it and  
20 then the resin, or vice versa, to the PTFE particles. In the alternative the drug and any excipient or other ingredient can be incorporated by first adsorbing it on the resin or on an inert support such as silica, absorbing it into the resin, or ionically bonding it to  
25 the resin. Sufficient inert liquid to form a putty-like mass can then be added. Preferably, about 100 parts by weight of the resin is used, about 40 parts by weight of the PTFE is used, and about 500 parts by weight of the inert liquid is used. Suitable liquids  
30 include chlorofluorocarbon and fluorocarbon liquids. Fluorocarbon liquids such as FLUORINERT™ FC5312 electronic fluid (3M) are preferred.

The resulting mixture is then stirred until it is of dough-like consistency and processed in a  
35 rubber mill as generally described in U.S. Pat. No. 4,153,661. Generally the processing involves biaxial fibrillation of the PTFE by repeatedly passing the mixture between the calendering rolls of the rubber

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mill. After each individual pass the resulting sheet is folded parallel to the axis of the calendering rolls into a layered structure, preferably a three-layered structure, rotated 90° and passed again through the calendering rolls. Preferably about 10 to about 20 passes are carried out in order to form a PTFE web having the resin substantially dispersed throughout. The resulting sheet is then passed through the rolls as required in order to form a sheet of the desired thickness. Once a sheet of the desired thickness is made, it can be air-dried at room temperature or placed in a convection oven at an appropriate temperature in order to remove the excess inert liquid. The final dry sheet device is preferably 0.2 mm to about 2 mm thick.

The flexible film backing can be applied using methods well known to those skilled in the art. A device in the form of a sheet material with a backing applied thereto can be made into a patch with a backing by die-cutting individual patches from the sheet. A patch can be of any suitable size and shape, e.g., a 1 cm<sup>2</sup> circular disk. In the case of a device having a backing applied from solution or suspension, individual patches can be arranged on a coating surface such that the portion of the patch that is intended to be adhered to the mucosa is in contact with the coating surface. The film backing material can be applied to the remainder of the patch by spraying, brushing or otherwise applying the film backing material.

While devices of the invention adhere to mucosal surfaces, they preferably exhibit substantially no instantaneous adhesion to dry skin. A device or a patch of the invention can therefore be handled by a patient without undue concern that the device or patch will have its mucosal adhesive properties compromised by adhering to the skin or to another dry surface prior to placement on the mucosa.

A device of the invention can be applied to a mucosal surface, such as the oral mucosa, e.g., the

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buccal mucosa or gingival mucosa, of a mammal and replaced as desired (e.g., as is necessary or as is convenient to the user) with a fresh patch, e.g., to maintain a therapeutically effective blood level of a drug. A device or a patch of the invention exhibits sustained release of a drug such that a therapeutically effective blood level of the drug can be achieved and/or maintained in a mammal for an extended period of time. Also, a therapeutic level of drug can be maintained in the vicinity of the mucosal surface (e.g., in the oral cavity or the vaginal cavity) if the treatment being effected is local rather than systemic.

#### Example 1

CARBOPOL™ 910 resin (50 g; B. F. Goodrich) was mixed with 16.7 g of PTFE (TEFLON™ 6-C polytetrafluoroethylene, DuPont) and 250 g of FLUORINERT™ 5312 electronic liquid (3M) to afford a substantially homogeneous putty-like mass. This mass was further mixed by hand with a spatula for about 1 minute. The mass was then formed into a film by successive passes between steel calendaring rolls (15 cm in diameter, 28 cm long) at 50°C using a nip gap of about 4 mm. After each pass, the resulting substantially rectangular film was z-folded parallel to the axis of the calendaring rolls and rotated 90° prior to the next pass. After these 15 initial passes the film was again repeatedly passed through the rolls, beginning with a nip gap of about 4 mm and closing the nip gap about 0.65 mm on each successive pass until the final sheet was about 0.3 mm thick. The final sheet was air-dried at room temperature to remove the excess liquid. Patches of about 1 cm<sup>2</sup> area were cut from the sheet with a 1 cm<sup>2</sup> circular die.

A flexible film backing was applied to several of the patches by spraying a 10% zein in ethanol/water solution directly on one side of the patch. The coated patches as well as patches without a

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backing were applied to the oral mucosa (the inside lip or to the gum) of several beagle dogs and visually observed at frequent intervals throughout the next 24 hours. All patches adhered equally well initially. By 5 2-3 hours post application, the patches without backings had swollen to 3-4 times greater size than the patches with backings and had become translucent due to the large amount of absorbed water. By about 4 hours post application, the patches without backings had 10 either fallen off the mucosa or were very loose and about to fall off. In contrast, the patches with backings were still very firmly attached to the tissue and they still retained their original opaque appearance. All of the patches with backings (4/4) 15 were firmly adhered at 12 hours post application and two of them were still attached at 24 hours post application.

These results show that these placebo patches adhere to oral mucosa. These results also show that 20 the presence of a backing improves adhesion and structural integrity.

#### Example 2

Using the general method of Example 1, except 25 that ethanol was used in place of the FLUORINERT electronic liquid, sheet material containing approximately 10% by weight PTFE, 85% by weight "polycarbophil", and 15% by weight theophylline was prepared. The theophylline was incorporated by 30 premixing with the polycarbophil.

The resulting sheet (approximately 15 cm long, 9 cm wide and 4.3 mm thick) was relatively stiff. The sheet was made more pliable by placing it in a dry glass dish and incubating it in the humid atmosphere of 35 a covered water bath for about 2 to 3 hours.



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In-vitro Dissolution

Three rectangular (8 mm by 10 mm) samples, each weighing approximately 167 mg, were cut from the sheet material. Each sample was weighted with a paper clip then placed in a vessel in a USP 2 dissolution apparatus. Each vessel was filled with 1000 mL of deionized, deaerated water and the paddle speed was set at 50 rpm. Samples were withdrawn at 1, 2, 4, 6, 8, 12, 16 and 20 hours. Theophylline content was determined by measuring absorbance at 271 nm. The table below shows the percent dissolved theophylline (assuming each sample contained approximately 25 mg of theophylline) at each time point. The values are the average of the values for the three vessels. The standard deviation is given for each entry.

Time (hr)	% Dissolved
1	40.2 $\pm$ 0.92
2	56.4 $\pm$ 1.22
4	74.8 $\pm$ 0.64
6	80.1 $\pm$ 1.05
8	81.4 $\pm$ 0.74
12	81.7 $\pm$ 0.80
16	81.9 $\pm$ 1.16
20	81.7 $\pm$ 1.88

In-vivo Delivery

The in-vivo drug delivery of the material was assessed in two female beagle dogs. Patches of 1.5 cm diameter and weighing 350 mg were cut from the sheet with a circular die. The patches had no occlusive backing so both sides were adherent. Both dogs were dosed (two patches for Dog A and one patch for Dog B)

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by applying the patches to the mucosal side of the lip just opposite the upper canine teeth. The patches adhered tightly and almost instantly. Venous blood samples (3 to 4 mL) were obtained from each dog at 0.5, 1, 2, 3, 4, 5, 6, 8 and 24 hours post dose. Plasma was separated from whole blood and stored frozen in glass vials until analysis. The dogs were fasted for about 16 hours prior to dosing and for about 6 hours post dosing; water was allowed ad libitum. The patches began to noticeably hydrate by 1 hour post dose. They swelled to approximately three times their original size. In Dog A, one of the two applied patches fell out between 6 and 8 hours post dose. At 8 hours post dose, the patch remaining in Dog A was removed. The patch in Dog B was removed at 24 hours post dose. No signs of irritation were noted in either dog's mouth.

Plasma concentrations of theophylline were determined by TDx™ assay (Abbott Laboratories). The results are given in the table below. A plasma level indicated as "low" means that the concentration of the detected substance is below the sensitivity of the assay and the identity of the substance detected is ambiguous.

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Theophylline Plasma Levels ( $\mu\text{g/mL}$ )		
Time (hr)	Dog A	Dog B
0.5	0.46	0.6
1	0.81	0.8
2	1.93	1.1
3	1.85	0.78
4	2.58	1.71
5	3.26	1.79
6	4.06	1.84
8	2.96	2.31
24	Low	1.71

The results set forth above show that a drug delivery device of the invention will release theophylline at a controlled rate and that a therapeutically effective blood level of theophylline can be obtained with a device without a backing.

#### Example 3

Using the general method of Example 2, sheet material was prepared which contained 4% by weight of digoxin, 20% by weight of PTFE and 76% by weight of CARBOPOL™ 910 resin.

#### In-vivo Delivery

The in-vivo drug delivery of the material was assessed in three female beagle dogs. Patches of 1.2 cm diameter and weighing approximately 26 mg were cut from the sheet with a die. The patches had no occlusive backing so both sides were adherent. All three dogs were dosed by applying a patch to the mucosal side of the upper lip next to the gums in the front of the muzzle. Venous blood samples (about 4 mL)

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were obtained from each dog prior to dosing and at 1, 2, 3, 4, 6, 8, 10, 12, 24 and 28 hours post dose. Plasma was separated from whole blood and stored frozen in glass vials until analysis. The dogs were not  
5 allowed food for 6 hours post dosing; water was allowed ad libitum. In Dog A it was noted that at 2 hours post dose the patch had slid down about halfway onto a tooth. Dog A spit out the patch between 2 and 3 hours post dose. The patch was replaced. The second patch  
10 was spit out between 8 and 10 hours post dose and was not replaced. Emesis was noted in Dog B between 2 and 3 hours post dose. Dog B spit out the patch between 6 and 8 hours post dose; it was not replaced. Dog C spit out the patch between 4 and 6 hours post dose; it was  
15 not replaced.

Plasma concentrations of digoxin were determined by TDx™ assay (Abbott Laboratories). A plasma level indicated as "low" means that the concentration of the substance detected is below the  
20 sensitivity of the assay and the identity of the substance is ambiguous. The lowest concentration on the standard curve was 0.2 ng/mL.

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Digoxin Plasma Levels (ng/mL)			
Time	Dog A	Dog B	Dog C
0	low	low	low
1	0.16	low	low
2	0.65	0.08	0.02
3	0.55	0.07	0.16
4	0.73	0.12	low
6	0.47	0.01	0.14
8	0.42	0.12	0.03
10	0.44	0.16	low
12	0.31	0.00	low
24	0.22	0.01	low
28	0.16	0.12	low

15           The results show that a therapeutically effective blood level of digoxin can be obtained with a device without a backing.

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## WHAT IS CLAIMED IS:

1. A transmucosal drug delivery device in the form of a sheet material having a surface intended to be adhered to a mucosal surface, comprising:
  - 1) a particulate polymeric resin comprising carboxylic acid containing monomer units and having an average particle size of less than or equal to about 100  $\mu\text{m}$ ;
  - 2) from about 10 parts to about 200 parts by weight of a polytetrafluoroethylene support matrix based on 100 parts by weight of the resin; and
  - 3) an amount of a drug effective to provide a desired therapeutic result;which composition contains less than about 10% water by weight based on the weight of the polymeric resin, and adheres to a mucosal surface for a time sufficient to release the drug to the mucosal surface.
2. A transmucosal drug delivery device according to Claim 1 further comprising a flexible film backing on one side of the device.
3. A transmucosal drug delivery device according to Claim 2, wherein the flexible film backing is substantially impermeable to the drug.
4. A transmucosal drug delivery device according to Claim 2, wherein the flexible film backing occludes substantially all of the surface area of the patch other than that surface that is intended to be adhered to the mucosal surface.
5. A transmucosal drug delivery device according to Claim 1, wherein the flexible film backing is substantially insoluble in fluids endogenous to the mucosal surface.

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6. A transmucosal drug delivery device according to Claim 2, wherein the flexible film backing comprises zein or ethylcellulose.

5 7. A transmucosal drug delivery device according to Claim 1, wherein the resin contains at least about 55% by weight of carboxylic acid moieties based on the total weight of the resin.

10 8. A transmucosal drug delivery device according to Claim 1, wherein the monomer is acrylic acid, maleic acid, itaconic acid, citraconic acid, or methacrylic acid, or a combination thereof.

15 9. A transmucosal drug delivery device according to Claim 1, wherein the monomer is acrylic acid.

20 10. A transmucosal drug delivery device according to Claim 1, wherein the resin has an average particle size of between about 1  $\mu\text{m}$  and about 80  $\mu\text{m}$ .

25 11. A transmucosal drug delivery device according to Claim 1, wherein the resin has a water content of less than about 6% based on the total weight of the resin.

30 12. A transmucosal drug delivery device according to Claim 1, comprising about 10 parts to about 100 parts by weight of a polytetrafluoroethylene support matrix, based on 100 parts by weight of the resin.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/04173

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC  
 Int.Cl. 5 A61K9/00; A61K9/70

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System

Classification Symbols

Int.Cl. 5

A61K

Documentation Searched other than Minimum Documentation  
 to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>

III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y	EP,A,0 068 777 (MINNESOTA MINING AND MANUFACTURING COMPANY) 5 January 1983 cited in the application see claims 1,2,5,6,8-10 see page 5, line 27 - page 6, line 5 see page 6, line 26 - line 32 -----	1-5,7-12
Y	EP,A,0 304 536 (THE B. F. GOODRICH COMPANY) 1 March 1989 see claim 1 see column 3, line 53 - column 4, line 57 -----	1-5,7-12

<sup>10</sup> Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

07 JULY 1993

Date of Mailing of this International Search Report

22. 07 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

VENTURA AMAT A.



**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9304173  
SA 74260

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07/07/93

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